UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/602,753	06/24/2003	Jeffrey A. Robl	HX0117A-CIP DIV 1	1055

23914 7590 12/16/2003

STEPHEN B. DAVIS
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000

EXAMINER	
HUANG, EVELYN MEI	
ART UNIT	**PAPER NUMBER**
1625	

DATE MAILED: 12/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/602,753	ROBL ET AL.	
	Examiner	Art Unit	
	Evelyn Huang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,14,15,17-36 and 41-44* is/are pending in the application.

4a) Of the above claim(s) *12,14,15,41,43 and 44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-36 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 12, 14, 15, 17-36, 41-44 are pending. Claims 1-11, 13, 16, 37-40, 45 are canceled according to the amendment filed on 6-24-2003.

Election/Restrictions

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 12, 14, 15, 41, drawn to species compounds, classified in class 546, subclass 93, and the method of use thereof.

II. Claims 17-36, 42, drawn to a composition comprising a compound of the recited structure in combination with other active ingredients, classified in class 514, subclass various dependent on the species elected, and the method of use thereof.

III. Claims 43, 44, drawn to an intermediate compound for making the compound in the composition.

The inventions are distinct, each from the other because of the following reasons:

Group I compounds, the intermediate compound of Group III and compounds in the composition and method of use are of different scopes. Furthermore, the method of Group I involves the use of the compound of Group I as the only active ingredient.

Invention I is drawn to a species compound. Invention II is drawn to a composition comprising the generic inventive compound as recited and other active ingredients. Invention III is drawn to an intermediate for making the generic inventive compound. The compound and the intermediate compound are related as mutually exclusive species in an intermediate-final product relationship. Distinctness is proven for claims in this relationship if the intermediate product is useful to make other than the final product (MPEP § 806.04(b), 3rd paragraph), and the species are patentably distinct (MPEP § 806.04(h)). In the instant case, the intermediate product is deemed to be useful in the preparation of the compound of formula I described by Schmeck (5932587) and the inventions are deemed patentably distinct since there is nothing on this record

to show them to be obvious variants. Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions anticipated by the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

3. During a telephone conversation with Mr. Rodney on 12-8-2003 a provisional election was made with traverse to prosecute the invention of Group II, claims 17-36, 42. Affirmation of this election must be made by applicant in replying to this Office action. Claims of Groups I, III ~~and~~ are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

4. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Priority

5. This is a divisional of U.S. Application No. 10/008154. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification of in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). The specific reference to any prior nonprovisional application must include the relationship (i.e., continuation, divisional, or continuation-in-part) between the applications except when the reference is to a prior application of a CPA assigned the same application number.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-36, 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 17,

- What are the '***other*** therapeutic agents' or '***other*** cardiovascular agents'? A definition is not found in the specification. The term 'including' is unclear since the therapeutic agents or cardiovascular agents other than those recited as being included have not been described.
- Are the 'platelet aggregation inhibitors' different from the 'anti-platelet agents' under the 'cardiovascular agents'?
- The term 'modulating' in 'lipid modulating agents' is unclear as to the positive or negative changes intended by the applicant. If only lipid-lowering agents are intended, it would be a duplicate of the earlier recited lipid-lowering agents.
- What are 'lipid agents'?

b. Claim 42,

- What are the 'related diseases'? A definition is not found in the specification. The rejection is applicable to claims dependent on the above claims.
- The term 'modulating' in 'lipid modulating agents' is unclear as to the positive or negative changes intended by the applicant
- What is the '***other*** type of therapeutic agent'?

The rejection is applicable to claims dependent on the above claims.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-36, 42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. ***.

a. *Nature of the invention.*

The instant invention is drawn to a composition comprising the inventive HMG-CoA-reductase inhibiting pyridinyl-containing tricyclic compound and other therapeutic agents, and its method of use in the treatment of the diseases related to cholesterol, diabetes, cardiovascular or cerebrovascular diseases as recited on pages 7-10 of the specification.

b. *State of the prior art and the level of the skill in the art.*

HMG-CoA reductase inhibitors useful for lowering cholesterol biosynthesis are described by Schmeck (5932587, US equivalent of EP 818197, PTO-1449), Chucholowski (4906624, PTO-1449), Robl I (5686433, PTO-1449) and Robl II (J. Med. Chem., PTO-1449). The myriads of diseases treatable and/or preventable with the HMG-CoA reductase inhibitor compounds as recited in the instant claims, such as Alzheimer's, cancer, dementia, HIV infection, etc., are not described in these references. The relationship between the inhibition of HMG-CoA reductase and these different diseases has not been fully established (Waldman A and Kritharides L, Drugs. 2003, 63(2): 139-152, especially page 146, 2.4 Conclusions, and page 149, 3.4 Conclusions). At present, there is no umbrella drug known to treat and/or prevent all these diseases.

Furthermore, drug-drug interactions, both antagonistic and synergistic, are well known in the pharmaceutical art. The side effects resulting from the interaction between HMG-CoA reductase inhibitors and other lipid-lowering agents, as well as the antagonistic/synergistic

effects of HMG-CoA reductase with additional therapeutic agent(s) have been described (Moghadasian MH, Life Sciences. 1999, 65(13):1329-1337, especially pages 1333-1334).

At the time of the invention, a composition comprising a HMG-CoA reductase inhibitor and anti-cancer agents, anti-Alzheimer's agents etc. has not been described.

The level of the skilled artisan in the HMG-CoA-reductase inhibitor art is high.

c. *The predictability/unpredictability of the art.*

The high degree of unpredictability is well recognized in the HMG-CoA reductase inhibitor art. A slight change in the structure of the compound would drastically change its biological activity as evidenced in the different IC_{50} values of the structurally similar HMG-CoA reductase inhibitors (Robl II, page 2809, Table III). There appears to be a lack of correlation between the in vitro and in vivo potencies of the compounds tested (Robl II, page 2810, column 1). The interaction between the inventive compound and the other therapeutic agents, with structures, modes of actions and utilities totally different from the instant, would be even more unpredictable.

d. *The amount of direction presented/working examples.*

An example composition comprising the inventive compound and other therapeutic agent(s) has not been described in the specification.

The procedures for measuring the HMG-CoA reductase inhibiting activity and the inhibition of cholesterol biosynthesis have not been described in the specification. In vivo procedures are not found in the specification.

e. *The breadth of the claims.*

The instant claims directed to the composition comprising the inventive compound and agents against myriads of diseases of diverse origins, and the method of use thereof. Applicant's claims does not commensurate with the scope of the objective enablement, especially in view of the high degree of unpredictability in the interaction between HMG-CoA inhibitors and other therapeutic agents, and the absence of working examples (paragraphs b-d above).

f. *Quantitation of experimentation necessary.*

Since insufficient teaching and guidance have been provided in the specification (paragraphs b-e above), one of ordinary skill in the art, even with relatively high level of skill, would not be able to use all the compounds as claimed without undue experimentation.

Conclusion

8. No claims are allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 703-305-7247. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Alan Rotman can be reached on 703-308-4698. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Evelyn Huang
Primary Examiner
Art Unit 1625

***